a compound of the present invention did not lead to elevated corticosterone levels like seen with semaglutide in a rat model and so possibly can be dosed to higher efficacy levels than GLP-1R-selective agents.

There remains a need to provide a compound that is a balanced co-agonist of GIP and GLP-1 receptors, but is selective against related glucagon and GLP-2 receptors. Also, there remains a need to provide a compound with balanced co-agonist activity of GIP and GLP-1 receptors which may provide weight loss given activity found in animal models. Additionally, there remains a need to provide a compound with balanced co-agonist activity of GIP and GLP-1 receptors that delivers adequate stability against DPP IV and other forms of degradation, but while still maintaining a low immunogenicity potential. Also, there remains a need to provide a compound with balanced co-agonist activity of GIP and GLP-1 receptors that supports potential once-weekly dosing in humans.

Accordingly, certain compounds of the present invention have lower potential for immunogenicity and injection site reactions than certain GIP-GLP-1 co-agonist compounds in the art. Certain compounds of the present invention have potential for producing weight loss in patients based on animal energy expenditure data. Furthermore, certain compounds of the present invention have a balanced co-agonist activity against GIP and GLP-1 receptors and selectivity against both glucagon and GLP-2 receptors, low immunogenicity potential, and pharmacokinetic (PK) characteristics that support once-weekly dosing in humans.

Summary

In one aspect of the present disclosure, there is provided a compound of Formula:

$YX_1EGTFTSDYSIX_2LDKIAQKAX_3VQWLIAGGPSSGAPPPS$;

wherein

X_1 is Aib;

X_2 is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_a$-CO-(CH$_2$)$_b$-CO$_2$H wherein a is 1 to 2 and b is 10 to 20;

X_3 is Phe or 1-Nal;

and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein with a pharmaceutically acceptable carrier, diluent, or excipient.

In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in therapy.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of type 2 diabetes mellitus.

In a further aspect of the present disclosure, there is provided a compound disclosed herein in simultaneous, separate, or sequential combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating type 2 diabetes mellitus, wherein the medicament is to be administered to a patient in need thereof.

Description

An embodiment of the present invention provides a compound of Formula I:

YX$_1$EGTFTSDYSIX$_2$LDKIAQKAX$_3$VQWLIAGGPSSGAPPPS;

wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_a$-CO-$(CH_2)_b$-CO_2H wherein a is 1 to 2 and b is 10 to 20; X_3 is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11), or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I, wherein X_1 is Aib; X_2 is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_a$-CO-$(CH_2)_b$-CO_2H wherein a is 1 to 2 and b is 10 to 18; X_3 is Phe; and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a compound of Formula I,

WE CLAIM:

1. A compound of Formula:

YX$_1$EGTFTSDYSIX$_2$LDKIAQKAX$_3$VQWLIAGGPSSGAPPPS;

wherein

X$_1$ is Aib;

X$_2$ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_a$-CO-(CH$_2$)$_b$-CO$_2$H wherein a is 1 to 2 and b is 10 to 20;

X$_3$ is Phe or 1-Nal;

and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein X$_3$ is Phe.

3. The compound of Claim 1, wherein X$_3$ is 1-Nal.

4. The compound of Claim 2 , wherein b is 14 to 18.

5. The compound of Claim 4, wherein b is 16 to 18.

6. The compound of Claim 5, wherein b is 18.

7. The compound of Claim 4, wherein a is 1.

8. The compound of Claim 4, wherein a is 2.

9. The compound of Claim 4, wherein the C-terminal amino acid is amidated as a C-terminal primary amide.

10. The compound of Claim 1, wherein

X$_1$ is Aib

X$_2$ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_1$-CO-(CH$_2$)$_{18}$-CO$_2$H;

X$_3$ is Phe;

and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3),

or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 1, wherein

X_1 is Aib

X_2 is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_2$-CO-$(CH_2)_{18}$-CO_2H;

X_3 is 1-Nal;

and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 4),

or a pharmaceutically acceptable salt thereof.

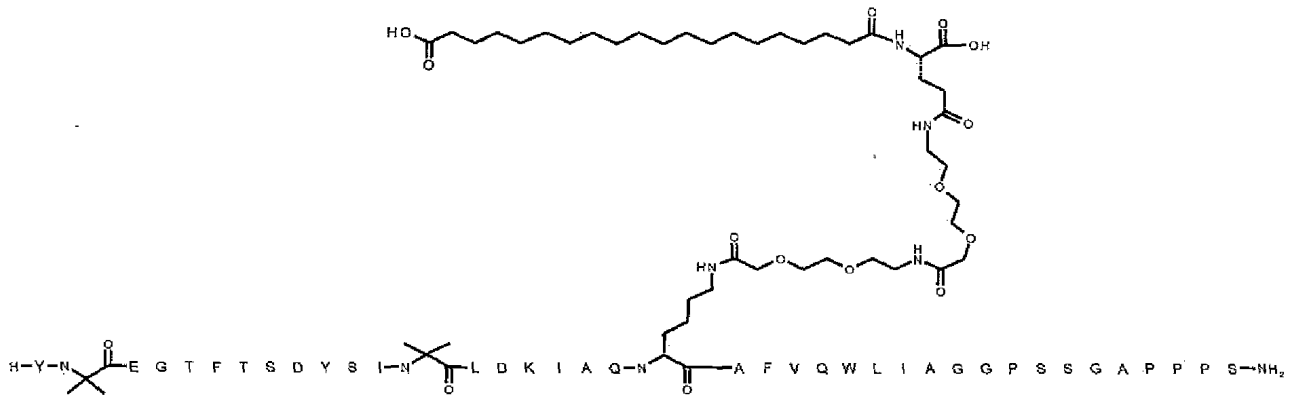
12. A pharmaceutical composition comprising the compound of Claim 10 with a pharmaceutically acceptable carrier, diluent, or excipient.

13. The compound of claim 11 for use in therapy.

14. The compounds of claim 11 for use in the treatment of type 2 diabetes mellitus.

15. The compound of claim 11 in simultaneous, separate, or sequential combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

16. The compound of Claim 1, wherein the Formula is:



17. A pharmaceutical composition comprising the compound of Claim 16 with a pharmaceutically acceptable carrier, diluent, or excipient.

18. Use of a compound of any one of claims 1-11 or 16 in the manufacture of a medicament for treating type 2 diabetes mellitus, wherein the medicament is to be administered to a patient in need thereof.

19. The use of Claim 18, wherein an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters is to be further administered simultaneously, separately, or sequentially in combination with the medicament.

20. The compound of Claim 16, for use in therapy.

21. The compound of Claim 16, for use in the treatment of type 2 diabetes mellitus.

22. The compound of Claim 16 in simultaneous, separate, or sequential combination with one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.